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Atypical familial juvenile hyperuricemic nephropathy associated with a hepatocyte nuclear factor-1β gene mutation

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Atypical familial juvenile hyperuricemic nephropathy associated with a hepatocyte nuclear factor-1β gene mutation.

Background. Familial juvenile hyperuricemic nephropathy (FJHN) is a dominantly inherited condition characterized by young-onset hyperuricemia, gout, and renal disease. The etiologic genes are unknown, although a locus on chromosome 16 has been identified in some kindreds. Mutations in the gene encoding hepatocyte nuclear factor (HNF)-1β have been associated with dominant inheritance of a variety of disorders of renal development, particularly renal cystic disease and early onset diabetes; hyperuricemia has been reported in some kindreds.

Methods. To assess a possible role for the *HNF-1*β gene in some FJHN kindreds we sequenced the *HNF-1*β gene in subjects from three unrelated FJHN families with atypical features of renal cysts or abnormalities of renal development. We also compared serum urate levels in subjects with HNF-1β mutations with populations of controls, type 2 diabetic subjects, and subjects with mild chronic renal failure without HNF-1β mutations.

Results. A splice-site mutation in intron 2, designated IVS2+1G>T, showed complete co-segregation with FJHN in one family with diabetes. Serum urate levels were significantly higher in the HNF-1β subjects compared with the normal control subjects (384 μmol/L vs. 264 μmol/L, $P = 0.002$) and the type 2 diabetic subjects (397 μmol/L vs. 271 μmol/L, $P = 0.01$). Comparison of serum urate levels in the HNF-1β subjects with gender-matched subjects with renal impairment of other causes did not reach significance (402 μmol/L vs. 352 μmol/L, $P = 0.2$).

Conclusion. Hyperuricemia and young-onset gout are consistent features of the phenotype associated with HNF-1β mutations, but the mechanism is uncertain. Families with HNF-1β mutations may fit diagnostic criteria for FJHN. Identification of HNF-1β patients by recognizing the features of diabetes and disorders of renal development is important in resolving the genetic heterogeneity in FJHN.

Key words: transcription factors, HNF-1β mutation, hyperuricemia, familial renal disease, juvenile gout.

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Familial juvenile hyperuricemic nephropathy [FJHN (MIM 162000)] is an autosomal-dominant condition associated with hyperuricemia, gout, and renal disease first described by Duncan and Dixon in 1960 [1]. FJHN affects young men, women, and children equally. Clinical gout is a variable feature [2–4], but hypertension and obesity are not characteristics of FJHN [2, 4, 5]. Renal impairment usually develops between 15 to 30 years of age with progression to end-stage renal failure (ESRF) within 10 to 15 years [4, 6]. Renal ultrasound appearances have been reported showing reduced renal size with abnormal echogenicity and occasionally renal cysts in some kindreds [7–9]. Examination of renal histology typically shows chronic tubulointerstitial inflammation with thickening and splitting of the tubular basement membranes. There is rarely evidence of urate crystal deposition [4, 6, 8, 10, 11]. Allopurinol may ameliorate the progression of the renal damage which makes presymptomatic diagnosis of the condition important, particularly in children [3, 12, 13].

There are two biochemical hallmarks of FJHN. The first is hyperuricemia disproportionate to the degree of renal dysfunction [2]. The second is a low urate clearance relative to creatinine, the fractional excretion of uric acid (FE_{ur}), of 5.1% ± 1.6% in men, women, and children [5, 14]. The hyperuricemia that results from the reduced FE_{ur} may precede the onset of renal disease [1, 5, 13]. The hypoexcretion of urate suggests that a defect in the transport of urate in the proximal renal tubule is of primary importance in the pathogenesis of this condition [5, 13, 15, 16]. Urate is freely filtered and approximately 90% is reabsorbed in the proximal tubule. There is bidirectional transport within the proximal tubule involving presecretory reabsorption, secretion and postsecretory reabsorption [4]. Two mechanisms exist for urate transport within the kidney, a voltage-sensitive urate transporter and a urate/anion exchanger [17, 18]. The rat

urate/anion transporter (rUAT) has been described in the rat [19, 20]. Human galectin 9 (hUAT) is homologous to the rUAT and it functions as a highly selective urate channel when inserted in lipid bilayers [21, 22]. The *hUAT* gene is 96% homologous to a novel gene *hUAT2,* which is also likely to be a urate transporter [22]. The URAT1 urate transporter encoded by *SLC22A12* has recently been described in human kidney [23].

No gene has been identified in the etiology of FJHN. Linkage analysis has identified a locus for FJHN on chromosome 16p12 in one Japanese kindred and 16p11.2 in two Czech families [9, 24]. Twelve other United Kingdom kindreds and a third Czech family failed to demonstrate linkage to this region, which supports a hypothesis of genetic heterogeneity within FJHN [9, 25]. The region identified on chromosome 16p11.2 is close to one locus for autosomal-dominant medullary cystic disease, MCKD2 on chromosome 16p12 (MIM 603860) [26]. It has been proposed that FJHN and MCKD2 may be two phenotypes arising from mutations in the same gene [11]. The *hUAT* and *hUAT2* genes have been mapped to between 17p11.2 and 17p12 on the short arm of chromosome 17 and the *SLC22A12* gene to chromosome 11q13 and all these genes may be further candidate genes for FJHN, although they are not within known areas of linkage [22, 23].

Hepatocyte nuclear factor (HNF)-1β mutations have been described in 12 kindreds and typically cause the renal cysts and diabetes (RCAD) syndrome [27, 28]. HNF-1β expression has been demonstrated in fetal human metanephric kidney [28]. A wide variety of developmental renal disorders have been described in association with HNF-1β mutations, including hypoplastic glomerulocystic kidney disease, cystic renal dysplasia, solitary functioning kidney, and oligomeganephronia [27, 29–31]. Consistent with a developmental abnormality renal abnormalities have been detected in a number of subjects in utero on antenatal ultrasound scanning [28–30]. Renal function in affected subjects ranges from normal to the development of ESRF in adolescence or young adulthood [30].

Hyperuricemia has been reported in subjects with HNF-1β mutations [32, 33]. In addition, three young women from separate families with different mutations within the UK HNF-1β collection have had gout (Coralie Bingham, unpublished data). Since renal cysts have been reported in a few FJHN families, along with impaired renal function, hyperuricemia, and gout, we hypothesized that HNF-1β mutations might be associated with FJHN and that hyperuricemia may be a consistent feature of HNF-1β mutations

METHODS

Subjects

The study population for genetic analysis consisted of members of three unrelated families (DUK504, DUK594, and DUK595) who form part of the FJHN collection of approximately 60 families held by the Guy's Hospital Purine Research Unit. These were atypical FJHN families with a history of renal cystic disease or evidence of abnormalities of renal development detected on ultrasound examination. One family also had a history of diabetes developing within the last 5 years (Fig. 1). The probands in these families were screened for HNF-1β gene mutations using direct sequencing (see below). When an HNF-1β mutation was found in the proband, genetic testing was performed in all consenting family members and their clinical data were reviewed. The study was approved by the local Ethics Committee and informed consent was obtained from each subject.

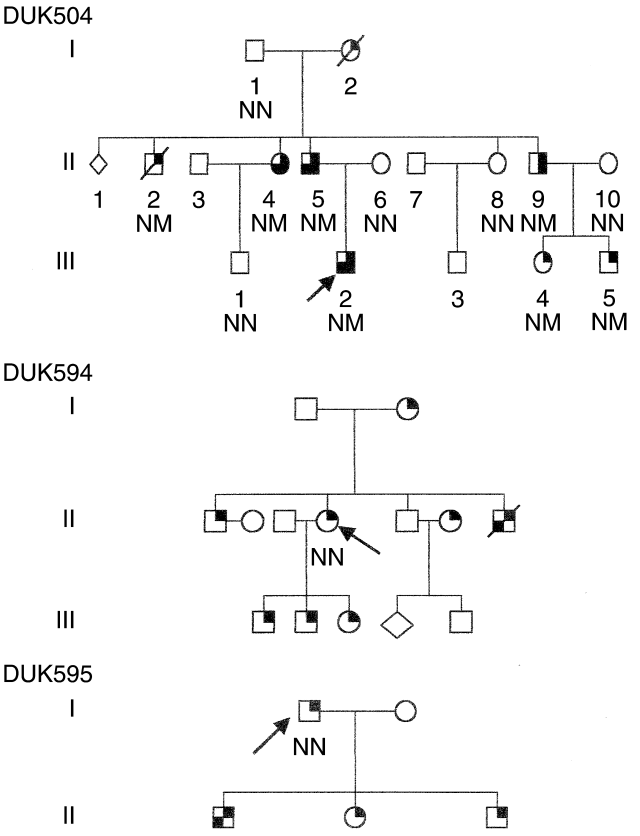

Fig. 1. Pedigrees of kindreds studied. Roman numerals on left of figure indicate generation number, and the numbers below the symbols indicate individuals within that generation. The HNF-1β genotype of each individual tested is indicated below the symbol: N, normal; M, mutated allele; FJHN, blackened upper right quadrant; diabetes, blackened lower right quadrant; renal cysts/disorder of renal development, blackened lower left quadrant. The proband in each kindred is marked with an arrow.

Clinical studies

To assess if hyperuricemia was a generalized feature of subjects with HNF-1β mutations, we measured serum urate levels in nine adult subjects with HNF-1β mutations from five families. Clinical details of five of these

subjects, but not their urate levels, have been published [27, 29, 30]. Serum urate levels were compared with control groups with type 2 diabetes, non-HNF-1β renal disease, and normal subjects. The subjects with type 2 diabetes and the normal controls were gender- and body mass index (BMI)-matched to the subjects with HNF-1β mutations. The subjects with non-HNF-1β renal disease were selected from general nephrology clinics. These subjects had a serum creatinine of <200 μmol/L and were gender-matched to eight of the HNF-1β subjects who had a serum creatinine of <200 μmol/L. Renal subjects were excluded if they gave a history of gout, or were on allopurinol. Statistical analysis was performed using unpaired Student *t* tests unless stated otherwise.

To study the excretion of uric acid the fractional excretion (FE_{ur}) was calculated from the uric acid clearance factored by the creatinine clearance × 100. The FE_{ur} was measured in the eight subjects with HNF-1β mutations who all had a serum creatinine of <200 μmol/L and in the three adult subjects from family DUK504 who were mutation carriers but were not in ESRF.

Mutation analysis of the *HNF-1β* gene

The entire promoter and coding regions of the 9 exons and the intron-exon boundaries of the *HNF-1*β gene were amplified by polymerase chain reaction (PCR) using genomic DNA from a single proband and sequence specific primers [34]. PCR was performed in a 25 μL volume containing 10 mmol/L Tris-HCl, pH 8.3, 50 mmol/L KCl, 1 to 1.5 mmol/L $MgCl_2$, 200 μmol/L desoxynucleoside triphosphate (dNTP), 2.5 pmol each primer, 0.25 U Amplitaq Gold Taq polymerase (Applied Biosystems, Warrington, UK), and 100 ng DNA. The cycling conditions were 15 minutes at 95°C followed by 35 cycles consisting of 1 minute at 94°C, 1 minute at 60°C, 2 minutes at 72°C. PCR products were purified using a QIAquick column (Qiagen, Crawley, UK) and both strands sequenced using a BigDye (version 2) Terminator Cycle Sequencing kit (Applied Biosystems) according to the manufacturer's recommendations. Reactions were analyzed on an ABI Prism™ 377 DNA Sequencer (Applied Biosystems). Sequencing data were analyzed using FACTURA™ and Sequence Navigator 1.0.1. software.

RESULTS

Identification of a mutation in the *HNF-1β* gene

A novel heterozygous mutation in the *HNF-1*β gene was identified in family DUK504. The mutation is at the conserved splice donor site of intron 2, designated IVS2+1G>T. The mutation is predicted to lead to a splicing defect with either exon skipping or intron retention, potentially resulting in premature termination if a frameshift is introduced. The mutation co-segregated with FJHN being present in seven of the affected subjects in the kindred (Fig.1). DNA was not available for testing from one deceased affected member of the kindred. To test evidence of linkage between FJHN and the mutation in the HNF-1β gene a logarithm of odds (LOD) score was computed assuming an autosomal-dominant mode of inheritance with full penetrance and a gene frequency of 0.0001 using Gene Hunter version 2 [35]. This gave a LOD score of 2.4, which was the maximum LOD score available with this family. The mutation was not present in 100 normal chromosomes analyzed by sequencing. No mutation in the HNF-1β gene was found in the two other United Kingdom families with FJHN.

Clinical characteristics

The clinical characteristics of family DUK504 are shown in Table 1. Seven of the affected subjects have hyperuricemia, five have reduced FE_{ur}, and three subjects have young-onset gout. This kindred also includes affected members with renal cysts ($N = 3$) and diabetes ($N = 4$). Antenatal ultrasound scanning of the proband (subject III2) was suggestive of bilateral pelviureteric junction obstruction. At the age of 7 months, an intravenous urogram confirmed that the left renal pelvis was distended with a pelviureteric junction obstruction, but that the right kidney was normal. He subsequently underwent a left pyeloplasty at the age of 2 years. A renal ultrasound scan at the age of 13 years showed that the left kidney was small and the right kidney was enlarged, containing three cysts and one to two echogenic foci suggestive of calculi. Subject I2 died at the age of 59 years in ESRF. She had previously required a pyeloplasty. Subject II2 was found to have renal calculi, he developed ESRF, and received a renal transplant. He has since died. Subject II4 had a renal biopsy performed at the age of 23 years. A generalized mild dilatation was noted of the proximal tubules with occasional tubules showing large cystic change. The appearances were mild and nonspecific other than elastosis of the blood vessels.

Clinical studies

The results are given as means ± standard deviation. The mean serum urate level was 384 (± 128) μmol/L in a group of United Kingdom adult subjects with HNF-1β mutations ($N = 9$) compared with 264 (± 54) μmol/L ($P = 0.002$) in a gender- and BMI-matched normal control population ($N = 18$). The HNF-1β subjects differed from the controls by having renal impairment (mean serum creatinine 176 ± 149 μmol/L vs. 68 ± 11 μmol/L) and more diabetes (66.7% vs. 0%, $P < 0.001$ Fisher's exact test). Further controls were selected to assess if renal impairment or diabetes accounted for the hyperuricemia observed. When the diabetic HNF-1β mutation carriers ($N = 6$) were compared with a gender- and BMI-matched population of type 2 diabetic subjects ($N = 24$), the mean serum urate remained elevated 397 (± 140)

Table 1. Clinical characteristics of kindred DUK504

Subject	I2	II2	II4	II5	II8	II9	III1	III2	III4	III5
Gender	Female	Male	Female	Male	Female	Male	Male	Male	Female	Male
Mutation status	NA	NM	NM	NM	NN	NM	NN	NM	NM	NM
Age at first study *years*	59	37	26	27	27	23	5	5	5	4
Gout	No	Yes	Yes	Yes	No	No	No	No	No	No
Age at onset of gout	—	21	23	27	—	—	—	—	—	—
Diabetes	No	No	Yes	Yes	No	Yes	No	Yes	No	No
Age at onset of diabetes	—	—	40	43	—	38	—	12	—	—
Renal diagnosis	ESRF, pyeloplasty	Renal calculi, ESRF	Renal cysts, non-specific interstitial scarring, calculus left kidney	Renal cysts				Renal cysts, pyeloplasty	Small kidneys	Small kidneys
P_{cr} *μmol/L*	550	430	124	115	84	169	45	77	67	61
CrCl *mL/min*	0.55	4	56	103	86	68	86	33	42	42
PUA *μmol/L*	260	470	430	360	160	550	173	340	325	286
UACl	0.37	2.4	3.8	6.4	13.8	4.0	12.2	3.8	4.6	5.1
FE_{ur} %	67	55.4	6.8	6.3	15.9	5.8	14.2	11.4	10.9	12.1

Abbreviations are: ESRF, end-stage renal failure; Per, plasma creatinine; CrCl, creatinine clearance; UACl, urate clearance.
Mutation status: NN, two normal alleles; NM, one normal, one mutated allele.
Reference ranges: Plasma uric acid (PUA) on a low purine diet by the enzymic method used: 100 to 260 μmol/L in children up to puberty; 130 to 260 μmol/L (adult female); and 150 to 300 μmol/L (adult male).
Fractional excretion of uric acid (FE_{ur}) 8.1% ± 3.2% (male), 12.8% ± 2.9% (female), and 18.4% ± 5.1% (children), [2].

Table 2. Fractional excretion of uric acid in 11 adult HNF-1β subjects

Family	Mutation	Gender	FE_{ur}%	Mean FE_{ur}%
DUK504	IVS2+1G>T	Male	6.3	5.0 ± 1.3
DUK504	IVS2+1G>T	Male	5.8	
DUK350	IVS2nt+3insT	Male	4.2	
DUK298[a]	P159fsdelT	Male	3.5	
DUK504	IVS2+1G>T	Female	6.8	8.5 ± 4.1
DUK350	IVS2nt+3insT	Female	5.6	
DUK350	IVS2nt+3insT	Female	7.1	
DUK350	IVS2nt+3insT	Female	4.6	
DUK507[a]	Q243fsdelC	Female	13.5	
DUK448[a]	S151P	Female	15.3	
DUK250[a]	P328L329fsdelCCTCT	Female	6.7	

[a] References 27, 29, and 30
Mean values given ± standard deviation. FE_{ur} reference range, 4.9% to 11.3% (male); 9.9%–15.7% (female).

μmol/L vs. 271 (± 94) μmol/L (P = 0.01). When the eight HNF-1β subjects with a creatinine <200 μmol/L (mean 127 ± 36 μmol/L) were compared with 32 gender-matched subjects with renal impairment not due to HNF-1β mutations (mean serum creatinine 117 ± 45 μmol/L), the mean serum urate was 402 (± 125) μmol/L vs. 352 (± 93) μmol/L (P = 0.2). The FE_{ur} results for 11 adult HNF-1β subjects are shown in Table 2. The mean FE_{ur} in the male subjects was 5.0% (± 1.3%), which is at the lower limit of the reference range (4.9% to 11.3%). The mean FE_{ur} in the female subjects was reduced at 8.5% (± 4.1%) with a reference range of 9.9% to 15.7%.

DISCUSSION

Family DUK504 has previously been reported as having FJHN [2, 5]; it fulfills the diagnostic criteria with hyperuricemia, reduced FE_{ur}, evidence of renal damage, and three members of the kindred with young-onset gout [2, 5]. Other conditions causing hyperuricemia, including enzymatic defects, hemolytic anemia or the use of drugs that interfere with urate metabolism, have been excluded [2]. Subjects III2, III4, and III5 were all diagnosed with FJHN in early childhood, following screening because of FJHN in a parent. Importantly, their renal function has improved with allopurinol treatment [12, 13]. This kindred also includes affected members with renal cysts and diabetes, the cardinal features of the RCAD syndrome associated with HNF-1β mutations [27, 28]. Families with HNF-1β mutations may therefore fit diagnostic criteria for FJHN in addition to having diabetes and disorders of renal development.

Hyperuricemia has previously been reported in subjects from two Japanese families with HNF-1β mutations [32, 33]. Upon reexamination of the other nine HNF-1β families in the United Kingdom collection, we found evidence of gout in young females (<40 years) in three kindreds (Coralie Bingham, unpublished data). Clinical gout is rare in young women as postpuberty women have a

higher FE_{ur} (12.8% ± 2.9%) compared with men (8.1% ± 3.2%), which results in lower serum urate levels in women [14]. This suggested that gout and hyperuricemia are a general feature of HNF-1β mutations.

Serum urate levels were significantly higher in a group of United Kingdom adult subjects with HNF-1β mutations compared with a gender- and BMI-matched normal control population. As 67% of the HNF-1β subjects had diabetes, which may be associated with hyperuricemia as part of the insulin resistance syndrome, we also compared the HNF-1β patients with a gender- and BMI-matched population of type 2 diabetic patients. Serum urate levels were significantly higher in the HNF-1β group. This would suggest that the hyperuricemia in the diabetic HNF-1β group of subjects is not just secondary to diabetes and insulin resistance. Comparison of a gender-matched population of subjects with renal impairment not due to HNF-1β mutations showed that the urate level was higher in the HNF-1β patients compared with the non-HNF-1β patients, but this difference failed to reach significance. The renal impairment in the HNF-1β group may therefore be contributing to their hyperuricemia independent of any direct mutational effect on urate transport. However, there is evidence from the FE_{ur} to support a possible direct mutational effect on urate transport. In chronic renal failure, the FE_{ur} increases as the glomerular filtration rate falls and there is a nonlinear increase of plasma urate with a linear increase in plasma creatinine. Thus, secondary clinical gout is very rare in patients with chronic renal failure [2, 4]. However, in our subjects the FE_{ur} is reduced (mean 8.5%) below the reference range (9.9% to 15.7%) in the female HNF-1β subjects with a serum creatinine <200 μmol/L and is close to the lower limit of the reference range in the male subjects (mean 5.0%) with a reference range of 4.9% to 11.3%, but the number of subjects was small.

Our results support the hypothesis that there is genetic heterogeneity within FJHN as we did not identify a mutation in the *HNF-1*β gene in two out of the three families tested, even though they were selected for phenotypic features suggestive of HNF-1β mutations. This and the other regions of linkage outside the HNF-1β region on 17cen-q 21.3 suggest that HNF-1β mutations are a minor cause of FJHN. We did not test other candidate genes or regions in these families. The two families without mutations had affected members with renal cystic disease or evidence of disordered renal development seen on ultrasound scanning in addition to hyperuricemia, but they did not have a history of diabetes. Early-onset diabetes or evidence of impaired glucose tolerance has been a feature in the majority (10/12) of the reported families with HNF-1β mutations [30]. It is interesting to note that two subjects in the DUK504 kindred had pelviureteric junction obstruction and required renal pyeloplasties. The pelviureteric junction region derives from the ureteric bud in the developing human embryo and this has been shown to be a site of HNF-1β expression [28]. A report of renal histology is only available from one subject and the original histology was not available for review.

The IVS2+1G>T mutation we report herein occurs at the conserved splice donor site of intron 2. A different mutation at this site, IVS2nt+1G>A, has been reported in a Japanese kindred where three affected members have renal cysts and diabetes and one subject has hyperuricemia [33]. These mutations are highly likely to be pathogenic and result in aberrant splicing. In order to make further predictions about the functional effects of these splice-site mutations, it would be necessary to perform studies on mRNA. The major sites of expression in the kidney, liver, pancreas, gut, and lung are not readily available for sampling from patients making further study difficult.

Our results suggest that all HNF-1β mutations cause hyperuricemia. The mechanism is unknown but may be a result of altered urate transport as well as chronic renal impairment. HNF-1β is structurally related to HNF-1α, which is another member of the homeodomain-containing superfamily of transcription factors [36]. In situ hybridization experiments in developing rat kidney have shown that both HNF-1β and HNF-1α are expressed in the renal proximal tubule. HNF-1β is expressed from the earliest inductory phases of development, HNF-1α appears later in the postinductory phase in cells committed to tubular differentiation [37]. The HNF-1α knockout mouse has evidence of renal proximal tubular dysfunction with a renal Fanconi syndrome with polyuria (85% body weight/day), aminoaciduria, phosphaturia, and glucosuria [38]. The defect in renal proximal tubular glucose resorption is caused by a significant reduction in expression of the high-capacity/low-affinity sodium-glucose transporter-2 (SGLT-2) [39]. HNF-1α probably has a role in the regulation of transcription of the *SGLT-2* gene mediated through HNF-1α binding sites. Human subjects with heterozygous HNF-1α mutations have a reduced renal threshold for glucose and thus develop glucosuria. This is likely to result from a direct effect of reduced HNF-1α activity leading to reduced transcription of the SGLT-2 glucose transporter [39–41]. It is possible to speculate that a similar mechanism may exist whereby reduced HNF-1β activity reduces transcription of the human urate transporters URAT1 and hUAT mediated through HNF-1β binding sites in the *SLC22A12* and *hUAT* genes. This hypothesis is difficult to test as the HNF-1β homozygous knockout mouse dies at 6.5 to 7.0 days postconception without developing visceral or parietal endoderm [42]. Screening of the sequence upstream of the *SLC22A12* gene in human and mouse for HNF-1 binding sites using *http://bindgene.ex.ac.uk* revealed a probable HNF-1 binding site. Screening upstream of the *UAT* gene found no clear evidence of binding sites.

CONCLUSION

We have identified a mutation in the *HNF-1*β gene in a single kindred with FJHN. This kindred also includes affected members with renal cysts and recently diabetes, the cardinal features of the RCAD syndrome that is associated with HNF-1β mutations. Absence of this mutation in the two other FJHN kindreds screened is further evidence for genetic heterogeneity within FJHN. Screening for HNF-1β mutations in FJHN is particularly appropriate in those kindreds with renal cystic disease or other abnormalities of renal development, especially where there is also a history of diabetes. Hyperuricemia and young-onset gout affecting both men and women are further features of the variable phenotype associated with HNF-1β mutations.

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